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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/685,823	10/09/00	FILVAROFF	E P1834

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EXAMINER	
JIANG, D	
ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/685,823	FILVAROFF, ELLEN H.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *17,19,20 and 41-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-16,18 and 21-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *1-44* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED OFFICE ACTION

Applicant's election without traverse of Group I invention, claims 1-40, and the species election of IL-1ra (from claim 18), in Paper No. 5, filed on 9 April 2001 is acknowledged. Accordingly, claims 17 and 19-20 (species), and 41-44, as non-elected species, or non-elected inventions, are withdrawn from consideration.

Currently, claims 1-16, 18, and 21-40 are under consideration.

This application is filed as a continuation in part (CIP) of prior application SN09/380,142, and the claims presented in this application are significantly different from the original claims of the '142 application. For the following reasons, the Examiner finds that claims 1-4, 8-16, 18, and 21-39 are not supported in the manner required by 35 U.S.C. 112 by the prior application, thus none of above is entitled to the benefit of the filling date of the prior application.

The priority application '142 teaches that "IL-17 likely contributes to loss of articular cartilage in arthritic joints, and thus inhibition of its activity might limit inflammation and cartilage destruction" (page 90, lines 22-23), and speculates that antagonists to IL-17 "may be useful for the treatment of inflammatory conditions and cartilage defects such as arthritis" (page 90, lines 27-30). However, the disclosure of the '142 application does not teach specifically the entire genus of cartilage disorders (as claims 1-3, 8-9, 13-16, 18, and 37-38), anti-IL-17 antibody as an IL-17 antagonist (claims 2, and 38), degenerative cartilagenous disorders (claims 1-4, and 39), injury-induced cartilagenous disorders (claims 10-12), a standard surgical technique, pharmaceutical compositions of IL-17 antagonists (claim 13) or combination therapy of a IL-17 antagonist and at least one cartilage agent (claims 15, 16, and 18), and a method of preventing cartilage damage (claims 21-36).

Claims 5-7, and 40 are entitled to the benefit of the filling date of prior application SN09/380,142.

Formal Matters:

Claims 1-16, 18, and 21-40 are objected to for encompassing a non-elected subject matter, an antagonist to LIF. The applicant is required to amend the claims to read only upon the elected invention.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-16, 18, and 21-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a method of treating rheumatoid arthritis (RA, for instance, claim 6), or osteoarthritis (OA, for instance, claim 7), does not reasonably provide enablement for with claims to a method of treating *any* or *all* cartilagenous disorders, degenerative cartilagenous disorders, or arthritis, or to a method of *preventing* these disorders including RA and OA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification discloses that "through the induction of a number of responses and cytokines, IL-17 is able to medicate a wide-range of effects, mostly *pro-inflammatory* and hematopoietic" (page 4, the second paragraph), "IL-17 also induces NO [nitric oxide] production in chondrocytes, and is expressed in arthritic, but not normal joints" (page 18, lines 36-37, reviewed in Martel-Pelletier et al., Front. Biosci., 4:d694-703, 1999, provided by the applicant), NO "is believed to play a role in the pathology of cartilagenous disorders, including arthritis" (page 64, lines 7-8), and "there exists a great need for agents which antagonize the action of IL-

17" (page 4, line 37). Additionally, the specification demonstrates effects of IL-17 upon explant or cell culture on cartilage matrix turnover and metabolism, induction of carbolic proteins, induction of NO, etc. (Examples 1-3). Further, the specification teaches anti-IL-17 antibodies, and a working example of treating rheumatoid arthritis in vivo, indicating anti-IL-17 antibodies decreased progression of arthritis during treatment (Example 4).

However, the disclosure provides no evidence that such treatment is beneficial to *any* or *all* of cartilagenous disorders (as claims 1-3, 8-9, 13-14, and 37-38), degenerative cartilagenous disorders (as claims 4, and 39), arthritis (as claims 5, and 40), cartilagenous disorders resulting from injury (as claims 10-12), or can *prevent* cartilage damage caused by any of cartilagenous disorders (as claims 21-36). As evidenced in the prior art and acknowledged in the disclosure itself, IL-17 is known as a *pro-inflammatory* cytokine, which leads to the suggestion that IL-17 may play a pivotal role in initiating and/or sustaing an inflammatory response (page 4, lines 25-26). However, not all cartilagenous disorders are inflammatory, and as also known in the art, cartilagenous disorders such as post-traumatic arthritis are considered non-inflammatory arthritis, to which IL-17 antagonists may not be therapeutic. The specification provides neither clear direction or enough guidance, nor working example to teach how to use the method to treat or prevent a commensurate number of the claimed cartilagenous disorders, such as those resulting from injury.

Given the reasons above, and the breadth of claims 1-5, 8-16, 18, and 21-40 in light of the nature of the invention which is an anti-inflammatory therapy, the state of the prior art which indicates not all cartilagenous disorders are inflammatory, the lack of predictability in the art, and the lack of direction or guidance and working examples other than for RA, provided by the invention, it would require undue experimentation for the skilled artisan to practice the invention as claimed.

Claims 21-36 are further not enabled for the limitation of "preventing" cartilage damage caused by a cartilagenous disorder. In searching the prior art, the results of record have not established that any of the related diseases can be prevented. All that has been shown is that certain diseases that are related to cartilagenous disorder can be treated. Prevention would necessarily mean that a patient would be given an IL-17 antagonist, and such administration would ensure that the patient did not develop these diseases. As such preventative effect has not

been shown, and a patient is most likely asymptomatic in the early stage of the damage, the asserted utility of *preventing* the diseases is not enabled. The language, such as "reducing further cartilage damage due to RA or OA", is suggested.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16, 18, and 21-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 8, 15, 18, 21, 28, 35, and 37 are indefinite for using the term "*effective* amount". It is unclear for what it is "effective".

Claim 15 is further indefinite because it is unclear what a "cartilage agent" is.

Claim 18 is further indefinite for using inclusive language "*and* variants thereof", which would indicate applying both "tetracyclines and variants thereof" simutaneously. The alternative term "or" is suggested.

Claim 21 is further indefinite because it is unclear what "preventing cartilage damage" is intended. Does it mean to prevent any damage, or only the further damage, as a pre-existing damage can not be prevented.

Claims 14 and 34 are indefinite because it is not clear what "a standard surgical technique" is.

Claim 16 is indefinite because it is unclear what a "catabolism antagonist" is.

Claims 22 and 38 are indefinite for using inclusive language "and" in "wherein the IL-17 *and* LIF are anti-IL-17 *and* anti-LIF antibodies", which reads on the IL-17 (or LIF) antagonist is anti-IL-17 and anti-LIF antibody. The alternative term "or" is suggested.

Claim 33 is indefinite and vague because it is unclear how "the effective *amount* of..." can "further comprises a carrier or ...".

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-9, 13, 14, 21-26, 28, 29, 33, 34, and 37-40 are rejected under 35 U.S.C. 102(a) as being anticipated by Troutt, WO 98/23284 (provided by the applicant).

Troutt discloses a method of treating OA or RA, comprising administering soluble IL-17R (a functional equivalent of IL-17 antagonist) in conjunction with other immunoregulatory molecues, such as IL-1Ra (page 2, the fourth paragraph; page 16, the fourth paragraph). The teachings of Troutt meet the limitations of claims 1-9, as a method of treating OA or RA (page 1, the last paragraph), claims 13 and 14, as a IL-17 antagonist with a carrier, and used with a "standard surgical technique" (page 16, the fifth paragraph), claims 14, 21-26, 28, 29, 33, and 34 (inherent property), claims 37-40 (OA or RA *patients* are mammals). The reference, therefore, anticipates these claims.

Claims 1-4, 8-9, 13, 14, 21-26, 28, 29, 33, 34, and 37-39 are rejected under 35 U.S.C. 102(a) as being anticipated by Shigeru et al., JP2000186046 (July 4, 2000).

Shigeru discloses that the levels of IL-17 in the synovial fluids of RA patients are significantly higher (Figure 4); and that IL-17 neutralizing antibody is able to inhibit IL-17-induced osteoclastogenesis (Figure 1), and is antirheumatic and antiarthritic (abstract). Further, the cited reference teaches a method of treating bone joint destruction, such as RA using an IL-17 neutralizing antibody (abstract), which is an antagonist to IL-17. Therefore, the method taught by Shigeru meets the limitations of claims 1-4, 8-9, 13, 14, and 37-39. Additionally, the cited reference anticipates claims 21-26, 28, 29, 33 and 34 because the preventing features recited in these claims would be inherent property of the IL-17 antibody.

With respect to claim 13, the anti-IL-17 antibodies used by Shigeru are dissolved in saline or buffer, therefore, the cited references anticipates the claim.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 13, 14, 21-26, 28, 29, 33, 34, and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chabaud et al. (J. Immunol., 1998, 161:409-414, provided by the applicant), in view of Carroll et al. (Inflammation Research, 47:1-7, 1998, provided by the applicant).

Chabaud discloses that "production of biologically active IL-17 was demonstrated in RA synovium supernatants", "RA synovium T cells producing IL-17 can activate mesenchymal cells leading to an increased proinflammatory pattern" (abstract), and a blocking anti-IL-17 antibody reduced production of IL-6 and LIF (Table III), which are mediators of inflammation, present at high concentration in RA synovial fluid, and involved in the pathogenesis of RA, as taught by Carroll. Further, Chabaud teaches that "control of the production and action of IL-17 may represent a therapeutic target for reducing the ehhancing effect of monocyte-derived cytokines (page 413, the last paragraph).

Neither Chabaud nor Carroll teaches to apply an IL-17 antagonist in vivo to treat a cartilagenous disorder, such as RA.

However, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to treat a patient with RA (a cartilagenous disorder or a degenerative

cartilagenous disorder of articular cartilage) by administering an effective amount of an antagonist to IL-17, as Chabaud has suggested (control the action of IL-17). One of ordinary skill in the art would have been motivated to do so at Chabaud's indication (anti-IL-17 antibody significantly reduces production of pro-inflammatory cytokines, IL-6 and LIF), and reasonably would have expected success because of the positive results from Chabaud's experimentation.

Additionally, the preventing features recited in claims 21-26, 28, 29, 33 and 34 would be inherent property of the IL-17 antibody.

Claims 1-4, 8-9, 13, 14, 21-26, 28, 29, 33, 34, and 37-39 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Kotake et al. (J. Clin. Invest., 1999, 103:1345-1352, provided by the applicant), and Chabaud et al. (Arthritis & Rheumatism, 1999, 42:963-970, provided by the applicant), in view of Carroll et al. (Inflammation Research, 47:1-7, 1998).

Kotake discloses that the concentration of IL-17 in the synovial fluids and synovial tissues was significantly elevated in RA patients, but not in OA or trauma patients, that IL-17 is a crucial cytokine for osteoclastic resorption in RA patients, and that anti-IL-17 antibody significantly inhibited osteoclast formation induced by culture media of RA synovial tissues (the abstract).

Chabaud discloses that a blocking anti-IL-17 antibody reduced production of IL-6 (abstract), which is a pro-inflammatory cytokine, present at high concentration in RA synovial fluid, and involved in the pathogenesis of RA, as taught by Carroll.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to design a method as claimed to treat a patient with RA (a cartilagenous disorder or a degenerative cartilagenous disorder of articular cartilage) by administering an effective amount of an antagonist to IL-17. One of ordinary skill in the art would have been motivated to do so at Kotake's and Chabaud's indication (anti-IL-17 antibody significantly inhibited osteoclast formation, and reduces production of pro-inflammatory cytokines, IL-6, and/or LIF), and reasonably would have expected success because of the positive results from Kotake's and Chabaud's experimentation.

Additionally, the preventing features recited in claims 21-26, 28, 29, 33 and 34 would be inherent property of the IL-17 antibody.

Claims 15, 16, 18, 35, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chabaud et al. (1998), and Arend et al. (Annu. Rev. Immunol., 1998, 16:27-55, provided by the applicant).

The teachings of Chabaud are reviewed above. Additionally, Chabaud teaches that IL-17 leads to an enhanced pro-inflammatory secretion profile when combined with IL-1 (Figures 3 and 4).

Arend teaches a method of treating patients with rheumatoid arthritis with IL-1Ra, and indicates improvement of these patients in clinical parameters and in radiographic evidence of joint damage (abstract).

Neither reference teaches to treat a cartilagenous disorder, such as RA, using the combined therapy of an IL-17 antagonist and IL-1Ra.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to treat a patient with RA (a cartilagenous disorder or a degenerative cartilagenous disorder of articular cartilage) by combining the IL-17 antagonist and at least one cartilage agent, such as IL-1Ra, based upon indications by Chabaud (synergistic effects of IL-17 and IL-1), and the positive results taught by Chabaud and Arend (IL-17 antibody, and IL-1Ra). One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because of potential additive or synergetic effects of the combination of the IL-17 antagonist and one cartilage agent, such as IL-1Ra, as Chabaud, and Arend teach that each agent has the potential therapeutic effect on rheumatoid arthritis.

Additionally, the preventing features recited in claims 35 and 36 would be inherent property of the IL-17 antibody and IL-1Ra.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

DJ
5/31/01